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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/823,257	LANDERS, JOHN E.
	Examin r	Art Unit
	Jeanine A Goldberg	1634

-- The MAILING DATE of this communication appears on the cov r sh et with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,24-28 and 65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,24-28 and 65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 903 .

4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed September 15, 2003 and October 17, 2003. Currently, claims 1-22, 24-28, 65 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is **FINAL.**

3. Any objections and rejections not reiterated below are hereby withdrawn in view of Applicant's response.

Priority

4. This application claims priority to provisional application 60-194,425, filed April 4, 2000.

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in-
> (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effect under this subsection of a national application published under section 122(b) only if the international application designating the United States was published under Article 21(2)(a) of such treaty in the English language; or
> (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

5. Claims 1-4, 6-7, 11, 14, 16, 18-19, 22-23, 25-28 and newly added Claim 65 are rejected under 35 U.S.C. 102(e) as being anticipated by Gentalen et al. (US Pat. 6,306,643, October 2001).

Gentalen teaches a method of using an array of probes in genetic analysis. Gentalen teaches methods which use multiple cells in an array containing different pooled mixtures of probes. Gentalen provides an example which detects a target nucleic acid having two polymorphic sites, each of which has two polymorphic forms (A/a and B/b). Four combinations of the probes exist (AB, aB, ab, Ab). The target sequence is analyzed by designing four cells each containing a different pool of two mixed probes. The pool of probes having both component probes matched with the target nucleic acid shows the highest binding (col. 9, lines 40-55)(limitations of Claim 1, 2, 3, 4, 11, 14, 22, 23). The supports typically have discrete spatially addressable regions or cells (col. 11, liens 15-16). (limitations of Claim 6, 7). The target nucleic acid can be genomic, mitochondrial DNA, RNA or cDNA (col. 10, lines 19-20, col. 6, lines 33-34)(limitations of Claim 25-28). The genomic DNA samples are usually subject to amplification before application to an array (col. 10, lines 22-23)(limitations of Claims 16-17). Methods which amplify genomic DNA samples prior to application to the array have reduced the complexity of the genome.

Response to Arguments

The response traverses the rejection. The response asserts that the claims have been amended to include the requirement that "only" the first allele of a first SNP of the polymorphic locus is analyzed. This argument has been reviewed but is not convincing

because Claim 22, which depends from Claim 1, which is presumed to further limit Claim 1, states that the first and second SNPs are analyzed simultaneously. Therefore, the claim directed to only detecting a first SNP followed by detecting a second SNP does not appear to be what is intended by Claim 1. Thus, since Claim 22 depends on Claim 1, Gentalen appears to anticipate the claimed invention. Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 6-7, 11, 14, 16, 18-22, 25, 27 and newly added Claim 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sapolsky et al (US Pat. 5,858,659, January 1999) in view of Murphy et al. (WO 99/09164, February 25, 1999).

Sapolsky et al. (herein referred to as Sapolsky) teaches a rapid efficient method for analyzing polymorphic markers using arrays (abstract). The arrays of Sapolsky are arranged in blocks which are capable of discriminating the three genotypes for a gene marker. Sapolsky teaches that providing a genetic linkage map allows one to identify a set of genetic markers that follow a specific trait (col. 1, lines 30-35). Sapolsky teaches the use of polymorphisms as genetic linkage markers is of critical importance in

locating, identifying and characterizing the genes which are responsible for specific traits (col. 1, lines 65-68). The arrays of oligonucleotides allows for screening large numbers of polymorphic markers in a genome (col. 2, lines 10-15). As seen in Figure 2, a single oligonucleotide array contains 78 separate detection blocks. The triplet layout of detection blocks for the polymorphism is illustrated. The tiled arrays include a number of detection blocks which are specific and complementary to each variant (col. 5, lines 20-26). The probes are synthesized in pairs differing at the biallelic base (col. 5, lines 25-28). Once an array is tiled for a set of polymorphisms, the target nucleic acid is hybridized with the array and scanned (col. 6, lines 5-15). Sapolsky demonstrates detection of DNA and RNA (col. 11-12). Sapolsky teaches the advantages of the method allow for rapid, automatable analysis of genetic linkage to even complex polygenic traits.

Sapolsky does not specifically teach that the method may be used on haplotypes.

However, Murphy et al. (herein referred to as Murphy) teaches a method of using DNA chips to immobilize oligonucleotides on a solid support to rapidly analyzed gene and their expression. Murphy describes a chip having "n" elements for performing allele specific sequence based techniques which has "n" different nucleotide sequences. The oligonucleotides of the chip are capable of specifically hybridizing to a haplotype of the BRCA2 DNA where at least one oligonucleotide is capable of specifically hybridizing to at each of the nucleotide positions recited. Table III, pages 38-39, contain the various haplotypes of BRCA2.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have used the SNP detection method of Sapolsky for detecting haplotypes comprising multiple SNP regions as taught by Murphy. While Sapolsky specifically suggest that analysis of multiple sets of markers in genetic linkage, Sapolsky does not explicitly teach analysis of specific SNPs which form a haplotype. However, Murphy specifically teaches five different haploytpes within the BRCA2 gene which contain various combinations of nucleotides. Murphy teaches a chip may be used to analyze the polymorphisms. Therefore, using the rapid, automatable analysis method of Sapolsky to detect specific combinations of SNPs which form a haplotype would have been obvious to the skilled artisan. Haplotypes have been found to contain more information than individual SNPs. Therefore, the ordinary artisan would have been motivated to have detected haplotypes using allele specific oligonucleotides on arrays.

Response to Arguments

The response traverses the rejection. The response asserts there is no motivation to combine Sapolsky and Murphy. This argument has been reviewed but is not convincing because Sapolsky specifically teaches identification of multiple markers. In the event that the argument is directed to the ability of the combination of Sapolsky and Murphy to differentiate between combinations of polymorphisms on a single strand of DNA, the claims are not so limited. During the interview, the applicant proposed a distinction between a SNP haplotype and a SNP genotype. The distinction relied upon detecting both maternal and paternal nucleic acids. However, the definition, as

provided in the specification, does not appear to be commensurate with the art. On page 11 of the instant specification, "haplotype" refers to the allelic constitution of a single chromosome or chromosomal region at two or more loci. Thus, only a single nucleic acid strand need to be determined to meet the definition in the specification. Thus, the arguments directed to the inability to detect haplotypes using the method of Sapolsky and Murphy is not persuasive. In the event that the claim were amended to recite determining the haplotype of each of the maternal and paternally inherited nucleic acids, the argument may be persuasive. Applicant is reminded that no new matter may be added to the claims.

Thus for the reasons above and those already of record, the rejection is maintained.

7. Claims 5, 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over or Sapolsky et al (US Pat. 5,858,659, January 1999) in view of Murphy et al. (WO 99/09164, February 25, 1999) as applied to Claims 1-4, 6-7, 11, 14, 16, 18, 19-22, 25, 27 above or Gentalen et al. (US Pat. 6,306,643, October 2001) in view of Newton (U.S. Patent 5,525,494, June 11, 1996).

Gentalen teaches a method of using an array of probes in genetic analysis. Gentalen teaches methods which use multiple cells in an array containing different pooled mixtures of probes. Gentalen provides an example which detects a target nucleic acid having two polymorphic sites, each of which has two polymorphic forms (A/a and B/b). Four combinations of the probes exist (AB, aB, ab, Ab). The target

sequence is analyzed by designing four cells each containing a different pool of two mixed probes. The pool of probes having both component probes matched with the target nucleic acid shows the highest binding (col. 9, lines 40-55)(limitations of Claim 1, 2, 3, 4, 11, 14, 22, 23). The supports typically have discrete spatially addressable regions or cells (col. 11, liens 15-16). (limitations of Claim 6, 7). The target nucleic acid can be genomic, mitochondrial DNA, RNA or cDNA (col. 10, lines 19-20, col. 6, lines 33-34)(limitations of Claim 25-28). The genomic DNA samples are usually subject to amplification before application to an array (col. 10, lines 22-23)(limitations of Claims 16-17). Methods which amplify genomic DNA samples prior to application to the array have reduced the complexity of the genome.

Neither Sapolsky in view of Murphy nor Gentalen specifically teach detecting SNP using a multiwell dish. Neither Sapolsky in view of Murphy nor Gentalen specifically teach using a spacer sequence to attach the probe to the solid support.

However, Newton teaches oligonucleotides are immobilized to a microtitre dish (a multiwell dish) for analysis of SNPs (limitations of Claim 5). Newton teaches attaching probes to a solid phase via an amino link on the 5' end of the final T of the poly T region (col. 11, lines 60-65)(limitations of Claim 9-10).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of detecting numerous SNPs using an array with the teachings of Newton that an array of nucleic acids may be analyzed in separate wells of a multiwell dish. The ordinary artisan would have recognized that using a multiwell dish would ensure the detection of SNPs using a solid support much like an array.

Additionally, the ordinary artisan would have recognized that probes may be attached to solid support via an amino link on the 5' end of the final T of the poly T region. Addition of spacer sequences enable the detection of oligonucleotides. The spacer allows the target nucleic acid to be a distince from the solid support which allows for increased binding. Therefore, the ordinary artisan would have been motivated to have added the polyT tail to enable attachment to the solid support.

Response to Arguments

The response traverses the rejection. The response asserts that for at least the reasons explained above, the rejection is not appropriate. This argument has been reviewed but is not convincing because the limitations of the instant claims have been met for the reasons above and those of record. Thus for the reasons above and those already of record, the rejection is maintained.

8. Claims 5, 8, 12-13, are rejected under 35 U.S.C. 103(a) as being unpatentable over Sapolsky et al (US Pat. 5,858,659, January 1999) in view of Murphy et al. (WO 99/09164, February 25, 1999) as applied to Claims 1-4, 6-7, 11, 14, 16, 18, 19-22, 25, 27 above or Gentalen et al. (US Pat. 6,306,643, October 2001) in view of Walt et al. (U.S. Patent 6,327,410, December 4, 2001).

Gentalen teaches a method of using an array of probes in genetic analysis. Gentalen teaches methods which use multiple cells in an array containing different pooled mixtures of probes. Gentalen provides an example which detects a target nucleic acid having two polymorphic sites, each of which has two polymorphic forms

(A/a and B/b). Four combinations of the probes exist (AB, aB, ab, Ab). The target sequence is analyzed by designing four cells each containing a different pool of two mixed probes. The pool of probes having both component probes matched with the target nucleic acid shows the highest binding (col. 9, lines 40-55)(limitations of Claim 1, 2, 3, 4, 11, 14, 22, 23). The supports typically have discrete spatially addressable regions or cells (col. 11, liens 15-16). (limitations of Claim 6, 7). The target nucleic acid can be genomic, mitochondrial DNA, RNA or cDNA (col. 10, lines 19-20, col. 6, lines 33-34)(limitations of Claim 25-28). The genomic DNA samples are usually subject to amplification before application to an array (col. 10, lines 22-23)(limitations of Claims 16-17). Methods which amplify genomic DNA samples prior to application to the array have reduced the complexity of the genome.

Neither Sapolsky in view of Murphy nor Gentalen does not specifically teach using surfaces such as multiwell dishes and beads.

However, Walt teaches a method of detecting target analytes using a surface which has been modified to contain physical configurations such as wells or small depressions in the substrate that can retain the beads such that a microsphere can rest in the well (col. 5, lines 60-65). As seen in Figure 5A and 5B, beads are located within a welled dish. Walt teaches that bioactive agents include nucleic acids. The nucleic acid may be DNA, both genomic and cDNA, RNA or any combination (col. 10, lines 30-33). Walt teaches that probes are designed to be complementary to a target sequence such that hybridization of the target and the probes of the present invention occurs (col. 10, lines 40-50). Each bead comprises a single type of bioactive agent (col. 11, lines 40-

50). Walt teaches using different dyes which allow for distinguishing between molecules (col. 13). Walt teaches that the methodology finds uses in detection of mutations or mismatches in target nucleic acids such as single nucleotide polymorphisms (col. 24, lines 53-60). Walt teaches that the use of the beads with bioactive agents allows the beads to be randomly distributed on the array, a fast and inexpensive process as compared to either the in situ synthesis or spotting techniques of the prior art (col. 4, lines 53-56).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the array surface of Sapolsky in view of Murphy or Gentalen to contain wells and beads as taught by Walt. The ordinary artisan would have been motivated to have designed the array surface according to Walt since Walt teaches that "the use of the beads with bioactive agents allows the beads to be randomly distributed on the array, a fast and inexpensive process as compared to either the in situ synthesis or spotting techniques of the prior art" (col. 4, lines 53-56).

9. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sapolsky et al (US Pat. 5,858,659, January 1999) in view of Murphy et al. (WO 99/09164, February 25, 1999) as applied to Claims 1-4, 6-7, 11, 14, 16, 18, 19-22, 25, 27 above or Gentalen et al. (US Pat. 6,306,643, October 2001) in view of Arnold et al. (U.S. Patent 6,410,231, June 25, 2002).

Gentalen teaches a method of using an array of probes in genetic analysis. Gentalen teaches methods which use multiple cells in an array containing different

pooled mixtures of probes. Gentalen provides an example which detects a target nucleic acid having two polymorphic sites, each of which has two polymorphic forms (A/a and B/b). Four combinations of the probes exist (AB, aB, ab, Ab). The target sequence is analyzed by designing four cells each containing a different pool of two mixed probes. The pool of probes having both component probes matched with the target nucleic acid shows the highest binding (col. 9, lines 40-55)(limitations of Claim 1, 2, 3, 4, 11, 14, 22, 23). The supports typically have discrete spatially addressable regions or cells (col. 11, liens 15-16). (limitations of Claim 6, 7). The target nucleic acid can be genomic, mitochondrial DNA, RNA or cDNA (col. 10, lines 19-20, col. 6, lines 33-34)(limitations of Claim 25-28). The genomic DNA samples are usually subject to amplification before application to an array (col. 10, lines 22-23)(limitations of Claims 16-17). Methods which amplify genomic DNA samples prior to application to the array have reduced the complexity of the genome.

Neither Sapolsky in view of Murphy nor Gentalen specifically teach using four different labels for each of the ASO probes.

However, Arnold teaches methods of detecting single nucleotide polymorphisms (SNPs) by capturing probes which contain different labels. Arnold provides an example for simultaneously probing for n different SNPs on a target with m alleles each exploits nxm differentially detectable labels. For example, for two SNPs each with two alleles, this embodiment exploit four differentially detectable labels measures as for instance, a Cy2/Cy7 ration for one SNP and a Cy3/Cy5 for the second SNP (col. 5, lines 35-45)(limitations of Claim 15).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the detection method of Sapolsky in view of Murphy or Gentelan with the teachings of Arnold to detect SNPs by using differential labels. The ordinary artisan would have been motivated to have used different labels for each distinct allele assayed for the expected benefit of ease of detection and definitive detection.

Response to Arguments

The response traverses the rejection. The response asserts that for at least the reasons explained above, the rejection is not appropriate. This argument has been reviewed but is not convincing because the limitations of the instant claims have been met for the reasons above and those of record. Thus for the reasons above and those already of record, the rejection is maintained.

10. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over or Sapolsky et al (US Pat. 5,858,659, January 1999) in view of Murphy et al. (WO 99/09164, February 25, 1999) as applied to Claims 1-4, 6-7, 11, 14, 16, 18, 19-22, 25, 27 above or Gentalen et al. (US Pat. 6,306,643, October 2001) in view of Pinkel et al. (US Pat. 6,210,878, April 3, 2001).

Gentalen teaches a method of using an array of probes in genetic analysis. Gentalen teaches methods which use multiple cells in an array containing different pooled mixtures of probes. Gentalen provides an example which detects a target nucleic acid having two polymorphic sites, each of which has two polymorphic forms (A/a and B/b). Four combinations of the probes exist (AB, aB, ab, Ab). The target

sequence is analyzed by designing four cells each containing a different pool of two mixed probes. The pool of probes having both component probes matched with the target nucleic acid shows the highest binding (col. 9, lines 40-55)(limitations of Claim 1, 2, 3, 4, 11, 14, 22, 23). The supports typically have discrete spatially addressable regions or cells (col. 11, liens 15-16). (limitations of Claim 6, 7). The target nucleic acid can be genomic, mitochondrial DNA, RNA or cDNA (col. 10, lines 19-20, col. 6, lines 33-34)(limitations of Claim 25-28). The genomic DNA samples are usually subject to amplification before application to an array (col. 10, lines 22-23)(limitations of Claims 16-17). Methods which amplify genomic DNA samples prior to application to the array have reduced the complexity of the genome.

Neither Sapolsky in view of Murphy nor Gentalen specifically teach using a reduced complexity genome.

However, Pinkel et al. (herein referred to as Pinkel) teaches an array based method which uses Cot-1 DNA to block repetitive sequences. Cot-1 is used to block the hybridization capacity of repetitive sequences.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the haplotyping methods of Sapolsky in view of Murphy or Gentalen to include an improved step of reducing the complexity of the genome, as taught by Pinkel. Pinkel teaches that hybridization capacity of repetitive sequences may be blocked using Cot-1 or human genomic DNA. The ordinary artisan would have been motivated to have blocked repetitive sequence to enable more sensitive detection. Prehybridization of the competitive Cot-1 DNA sequence will render

the repetitive sequences unavailable for hybridization in the subsequent hybridization reaction to the array, thereby resulting in low background.

Response to Arguments

The response traverses the rejection. The response asserts that for at least the reasons explained above, the rejection is not appropriate. This argument has been reviewed but is not convincing because the limitations of the instant claims have been met for the reasons above and those of record. Thus for the reasons above and those already of record, the rejection is maintained.

11. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sapolsky et al (US Pat. 5,858,659, January 1999) in view of Murphy et al. (WO 99/09164, February 25, 1999) as applied to Claims 1-4, 6-7, 11, 14, 16, 18, 19-22, 25, 27 above or Gentalen et al. (US Pat. 6,306,643, October 2001) in view of Caskey.

Gentalen teaches a method of using an array of probes in genetic analysis. Gentalen teaches methods which use multiple cells in an array containing different pooled mixtures of probes. Gentalen provides an example which detects a target nucleic acid having two polymorphic sites, each of which has two polymorphic forms (A/a and B/b). Four combinations of the probes exist (AB, aB, ab, Ab). The target sequence is analyzed by designing four cells each containing a different pool of two mixed probes. The pool of probes having both component probes matched with the target nucleic acid shows the highest binding (col. 9, lines 40-55)(limitations of Claim 1, 2, 3, 4, 11, 14, 22, 23). The supports typically have discrete spatially addressable

regions or cells (col. 11, liens 15-16). (limitations of Claim 6, 7). The target nucleic acid can be genomic, mitochondrial DNA, RNA or cDNA (col. 10, lines 19-20, col. 6, lines 33-34)(limitations of Claim 25-28). The genomic DNA samples are usually subject to amplification before application to an array (col. 10, lines 22-23)(limitations of Claims 16-17). Methods which amplify genomic DNA samples prior to application to the array have reduced the complexity of the genome.

Neither Sapolsky in view of Murphy nor Gentalen specifically teaches using two different capture methods.

It is noted that, as written, the claims encompass performing the method twice using two different methods.

However, Caskey teaches a method of detecting single base extension reactions with a polymerase and terminating nucleotides, the terminating nucleotides being mutually distinguishable and observing the identity of the nucleotide to thereby analyze the sequence. The arrays may be "read" by determining the identity and the location of each terminating nucleotide within the array on the solid support. The label and position of each terminating nucleotide on the solid support directly defines the sequence of the polynucleotide of interest that is being analyzed.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have performed the method of Sapolsky in view of Murphy or the method of Gentelan in combination with the method of Caskey to confirm the results obtained in one of the methods. Performing two assays to determine the identity of a location provides a more confident result. The probe methods of Sapolsky

and Gentelan require the hybridization of specific sequences, wherease the method of Caskey requires the efficiency of a polymerase. Therefore, the two methods have different reagents and would allow for more confident results if the two methods were combined.

Response to Arguments

The response traverses the rejection. The response asserts that for at least the reasons explained above, the rejection is not appropriate. This argument has been reviewed but is not convincing because the limitations of the instant claims have been met for the reasons above and those of record. Thus for the reasons above and those already of record, the rejection is maintained.

New Grounds of Rejection Necessitated by the IDS filed September 15, 2003

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-3, 5-8, 11-12, 14, 18-22, 24, 65 are rejected under 35 U.S.C. 102(e) as being anticipated by Dapprich et al (herein referred to Dapprich 1)(WO 01/42510 A2,

June 14, 2001) or Dapprich et al (herein referred to Dapprich 2)(US PGPub 20010031467, October 18, 2001).

The page numbers within this rejection correspond to Daprrich 1, namely the WO 01/42510 A2 document.

Dapprich et al. (herein referred to as Dapprich) teaches a method for isolating nucleic acids and determining haplotypes. Dapprich teaches that the targeting element is a molecule that binds specifically to a nucleic acid sequence in a population (page 2, lines 22-24). The targeting element is used to bind to a target nucleic acid sequence for detecting a distinguishing element (page 2, lines 31-33). Dapprich teaches that the targeting element binds within 100, 50, ...1 or 0 nucleotides of the distinguishing element. Thus, Dapprich teaches that the targeting element, namely a nucleic acid, binds on the distinguishing element, namely an ASO probe (page 3, lines 28-30)(limitations of Claim 1, 11-12). Dapprich teaches that an oligonucleotide may be chose such that is partially overlap a polymorphic site during hybridization to the fragments, with the mismatch preferentially located at or near the 3' end of the oligonucleotide (page 8, lines 25-30). Further Dapprich teaches that the targeting element may bind to a target nucleic acid sequence with an intervening sequence partly overlapping with the distinguishing element (page 3, lines 24-28). Dapprich also teaches that an extendable primer may be used to detect the distinguishing site (page 4, lines 6-8)(limitations of Claim 2, 14). Dapprich teaches a separation group can be any moiety that facilitates subsequent isolation and separation of an attached target element that is itself associated with a target nucleic acid (page 3, lines 8-12). The

targeting element with the attached separation group may be immobilized to a substrate forming an immobilized targeting element-separation group complex for at least one nucleic acid sequence (page 4, lines 25-30)(limitations of Claim 3, 18). Dapprich teaches that the method allows for the correlation of an unlimited number of sites constituting a haplotype (page 5, lines 10-15). Specifically, Dapprich teaches that the method allows for the separation of DNA fragments of maternal and paternal origin so that differences between the fragments can be assessed for the determination of a haplotype (page 7, lines 19-22). The method can be used to separate DNA into fractions that contain the separated alleles only, and overlapping heterozygous regions of different fragments can be used to assemble information on coinherited genomic regions spanning contiguous fragments (page 16, lines 13-18). Dapprich teaches that any distinguishing reaction that creates an allele-specific separation element enables the separation of targeted and non-targeted fragments (page 11). Dapprich teaches that the substrate includes particles, beads, magnetic beads, microtitreplates, glass slides, papers, test strips, gels (page 3, lines 15-20)(limitations of Claims 5-8).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 4, 13, 15-16, are rejected under 35 U.S.C. 103(a) as being unpatentable over Dapprich et al (herein referred to Dapprich 1)(WO 01/42510 A2, June 14, 2001) or Dapprich et al (herein referred to Dapprich 2)(US PGPub 20010031467, October 18, 2001) each in view of Arnold et al. (US Pat 6,410,231 B1, June 25, 2002).

Dapprich et al. (herein referred to as Dapprich) teaches a method for isolating nucleic acids and determining haplotypes. Dapprich teaches that the targeting element is a molecule that binds specifically to a nucleic acid sequence in a population (page 2, lines 22-24). The targeting element is used to bind to a target nucleic acid sequence for detecting a distinguishing element (page 2, lines 31-33). Dapprich teaches that the targeting element binds within 100, 50, ...1 or 0 nucleotides of the distinguishing element. Thus, Dapprich teaches that the targeting element, namely a nucleic acid, binds on the distinguishing element, namely an ASO probe (page 3, lines 28-30)(limitations of Claim 1, 11-12). Dapprich teaches that an oligonucleotide may be chose such that is partially overlap a polymorphic site during hybridization to the fragments, with the mismatch preferentially located at or near the 3' end of the oligonucleotide (page 8, lines 25-30). Further Dapprich teaches that the targeting element may bind to a target nucleic acid sequence with an intervening sequence partly overlapping with the distinguishing element (page 3, lines 24-28). Dapprich also teaches that an extendable primer may be used to detect the distinguishing site (page 4, lines 6-8)(limitations of Claim 2, 14). Dapprich teaches a separation group can be any moiety that facilitates subsequent isolation and separation of an attached target element that is itself associated with a target nucleic acid (page 3, lines 8-12). The

targeting element with the attached separation group may be immobilized to a substrate forming an immobilized targeting element-separation group complex for at least one nucleic acid sequence (page 4, lines 25-30)(limitations of Claim 3). Dapprich teaches that the method allows for the correlation of an unlimited number of sites constituting a haplotype (page 5, lines 10-15). Specifically, Dapprich teaches that the method allows for the separation of DNA fragments of maternal and paternal origin so that differences between the fragments can be assessed for the determination of a haplotype (page 7, lines 19-22). The method can be used to separate DNA into fractions that contain the separated alleles only, and overlapping heterozygous regions of different fragments can be used to assemble information on coinherited genomic regions spanning contiguous fragments (page 16, lines 13-18). Dapprich teaches that any distinguishing reaction that creates an allele-specific separation element enables the separation of targeted and non-targeted fragments (page 11). Dapprich teaches that the substrate includes particles, beads, magnetic beads, microtitreplates, glass slides, papers, test strips, gels (page 3, lines 15-20)(limitations of Claims 5-8).

Dapprich does not specifically teach the use of two separate ASO probes fixed to a surface, labeling of ASO probes.

However, Arnold teaches methods of detecting single nucleotide polymorphisms (SNPs) by capturing probes which contain different labels. Arnold specifically teaches capturing a nucleic acid with a first probe and detecting a second nucleic acid with an ASO probe. Arnold provides an example for simultaneously probing for n different SNPs on a target with m alleles each exploits nxm differentially detectable labels. For

example, for two SNPs each with two alleles, this embodiment exploit four differentially detectable labels measures as for instance, a Cy2/Cy7 ration for one SNP and a Cy3/Cy5 for the second SNP (col. 5, lines 35-45)(limitations of Claim 13, 15, 18). Arnold teaches using PCR fragments for detecting the various variations (col. 9, lines 35-60).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the teachings of Dapprich in view of Arnold. The method of Dapprich is directed to detecting multiple SNP on a single nucleic acid to determine the haplotype. Dapprich teaches using probes overlapping the SNP and primer extension to determine the identity of the SNP followed by immobilization. Arnold specifically teaches that once a nucleic acid is immobilized, further determination of the sequence, namely a SNP, may be determined using an ASO probe. It would have been prima facie obvious at the time the invention was made to have immobilized the probes of Dapprich prior to detecting the nucleic acid, as taught by Arnold. Thus, the ASO probes of Dapprich would be immobilized to the solid support followed by hybridization with a target nucleic acid (limitations of Claim 4).

14. Claims 9-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dapprich et al (herein referred to Dapprich 1)(WO 01/42510 A2, June 14, 2001) or Dapprich et al (herein referred to Dapprich 2)(US PGPub 20010031467, October 18, 2001) each in view of in view of Newton (U.S. Patent 5,525,494, June 11, 1996).

Dapprich et al. (herein referred to as Dapprich) teaches a method for isolating nucleic acids and determining haplotypes. Dapprich teaches that the targeting element is a molecule that binds specifically to a nucleic acid sequence in a population (page 2, lines 22-24). The targeting element is used to bind to a target nucleic acid sequence for detecting a distinguishing element (page 2, lines 31-33). Dapprich teaches that the targeting element binds within 100, 50, ...1 or 0 nucleotides of the distinguishing element. Thus, Dapprich teaches that the targeting element, namely a nucleic acid, binds on the distinguishing element, namely an ASO probe (page 3, lines 28-30)(limitations of Claim 1, 11-12). Dapprich teaches that an oligonucleotide may be chose such that is partially overlap a polymorphic site during hybridization to the fragments, with the mismatch preferentially located at or near the 3' end of the oligonucleotide (page 8, lines 25-30). Further Dapprich teaches that the targeting element may bind to a target nucleic acid sequence with an intervening sequence partly overlapping with the distinguishing element (page 3, lines 24-28). Dapprich also teaches that an extendable primer may be used to detect the distinguishing site (page 4, lines 6-8)(limitations of Claim 2, 14). Dapprich teaches a separation group can be any moiety that facilitates subsequent isolation and separation of an attached target element that is itself associated with a target nucleic acid (page 3, lines 8-12). The targeting element with the attached separation group may be immobilized to a substrate forming an immobilized targeting element-separation group complex for at least one nucleic acid sequence (page 4, lines 25-30)(limitations of Claim 3). Dapprich teaches that the method allows for the correlation of an unlimited number of sites constituting a

haplotype (page 5, lines 10-15). Specifically, Dapprich teaches that the method allows for the separation of DNA fragments of maternal and paternal origin so that differences between the fragments can be assessed for the determination of a haplotype (page 7, lines 19-22). The method can be used to separate DNA into fractions that contain the separated alleles only, and overlapping heterozygous regions of different fragments can be used to assemble information on coinherited genomic regions spanning contiguous fragments (page 16, lines 13-18). Dapprich teaches that any distinguishing reaction that creates an allele-specific separation element enables the separation of targeted and non-targeted fragments (page 11). Dapprich teaches that the substrate includes particles, beads, magnetic beads, microtitreplates, glass slides, papers, test strips, gels (page 3, lines 15-20)(limitations of Claims 5-8).

Dapprich does not teach using a spacer sequence to attach the probe to the solid support.

Newton teaches attaching probes to a solid phase via an amino link on the 5' end of the final T of the poly T region (col. 11, lines 60-65)(limitations of Claim 9-10).

Additionally, the ordinary artisan would have recognized that probes may be attached to solid support via an amino link on the 5' end of the final T of the poly T region. Addition of spacer sequences enable the detection of oligonucleotides. The spacer allows the target nucleic acid to be a distance from the solid support which allows for increased binding. Therefore, the ordinary artisan would have been motivated to have added the polyT tail to enable attachment to the solid support.

15. Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dapprich et al (herein referred to Dapprich 1)(WO 01/42510 A2, June 14, 2001) or Dapprich et al (herein referred to Dapprich 2)(US PGPub 20010031467, October 18, 2001) each in view of Pinkel et al. (US Pat. 6,210,878, April 3, 2001).

Dapprich et al. (herein referred to as Dapprich) teaches a method for isolating nucleic acids and determining haplotypes. Dapprich teaches that the targeting element is a molecule that binds specifically to a nucleic acid sequence in a population (page 2, lines 22-24). The targeting element is used to bind to a target nucleic acid sequence for detecting a distinguishing element (page 2, lines 31-33). Dapprich teaches that the targeting element binds within 100, 50, ...1 or 0 nucleotides of the distinguishing element. Thus, Dapprich teaches that the targeting element, namely a nucleic acid, binds on the distinguishing element, namely an ASO probe (page 3, lines 28-30)(limitations of Claim 1, 11-12). Dapprich teaches that an oligonucleotide may be chose such that is partially overlap a polymorphic site during hybridization to the fragments, with the mismatch preferentially located at or near the 3' end of the oligonucleotide (page 8, lines 25-30). Further Dapprich teaches that the targeting element may bind to a target nucleic acid sequence with an intervening sequence partly overlapping with the distinguishing element (page 3, lines 24-28). Dapprich also teaches that an extendable primer may be used to detect the distinguishing site (page 4, lines 6-8)(limitations of Claim 2, 14). Dapprich teaches a separation group can be any moiety that facilitates subsequent isolation and separation of an attached target element that is itself associated with a target nucleic acid (page 3, lines 8-12). The

targeting element with the attached separation group may be immobilized to a substrate forming an immobilized targeting element-separation group complex for at least one nucleic acid sequence (page 4, lines 25-30)(limitations of Claim 3). Dapprich teaches that the method allows for the correlation of an unlimited number of sites constituting a haplotype (page 5, lines 10-15). Specifically, Dapprich teaches that the method allows for the separation of DNA fragments of maternal and paternal origin so that differences between the fragments can be assessed for the determination of a haplotype (page 7, lines 19-22). The method can be used to separate DNA into fractions that contain the separated alleles only, and overlapping heterozygous regions of different fragments can be used to assemble information on coinherited genomic regions spanning contiguous fragments (page 16, lines 13-18). Dapprich teaches that any distinguishing reaction that creates an allele-specific separation element enables the separation of targeted and non-targeted fragments (page 11). Dapprich teaches that the substrate includes particles, beads, magnetic beads, microtitreplates, glass slides, papers, test strips, gels (page 3, lines 15-20)(limitations of Claims 5-8).

Dapprich does not specifically teach using a reduced complexity genome.

However, Pinkel et al. (herein referred to as Pinkel) teaches an array based method which uses Cot-1 DNA to block repetitive sequences. Cot-1 is used to block the hybridization capacity of repetitive sequences.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the haplotyping methods of Dapprich to include an improved step of reducing the complexity of the genome, as taught by Pinkel.

Pinkel teaches that hybridization capacity of repetitive sequences may be blocked using Cot-1 or human genomic DNA. The ordinary artisan would have been motivated to have blocked repetitive sequence to enable more sensitive detection. Prehybridization of the competitive Cot-1 DNA sequence will render the repetitive sequences unavailable for hybridization in the subsequent hybridization reaction to the array, thereby resulting in low background.

16. Claims 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dapprich et al (herein referred to Dapprich 1)(WO 01/42510 A2, June 14, 2001) or Dapprich et al (herein referred to Dapprich 2)(US PGPub 20010031467, October 18, 2001) each in view of Gentalen et al. (US Pat. 6,306,643, October 2001).

Dapprich does not specifically teach using RNA, cDNA, genomic DNA or mitochondrial genome as a nucleic acid sample.

However, Gentalen teaches a method of using an array of probes in genetic analysis. Gentalen teaches methods which use multiple cells in an array containing different pooled mixtures of probes. Gentalen provides an example which detects a target nucleic acid having two polymorphic sites, each of which has two polymorphic forms (A/a and B/b). Four combinations of the probes exist (AB, aB, ab, Ab). The target sequence is analyzed by designing four cells each containing a different pool of two mixed probes. The pool of probes having both component probes matched with the target nucleic acid shows the highest binding (col. 9, lines 40-55)(limitations of Claim 1, 2, 3, 4, 11, 14, 22, 23). The supports typically have discrete spatially addressable

regions or cells (col. 11, liens 15-16). (limitations of Claim 6, 7). The target nucleic acid can be genomic, mitochondrial DNA, RNA or cDNA (col. 10, lines 19-20, col. 6, lines 33-34)(limitations of Claim 25-28). The genomic DNA samples are usually subject to amplification before application to an array (col. 10, lines 22-23)(limitations of Claims 16-17). Methods which amplify genomic DNA samples prior to application to the array have reduced the complexity of the genome.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have used any sample available for detection of haplotypes using the method of Dapprich since Gentalen teaches target nucleic acids may be any of a variety of samples.

Conclusion

17. No claims allowable over the art.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 6:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571)272-0507

J. Goldberg
Jeanine Goldberg
Patent Examiner
January 22, 2004

Jehanne Sitton
Primary Examiner
1/22/04